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(21) International Application Number: PCT/US98/12605 (22) International Filing Date: 18 June 1998 (18.06.98) (30) Priority Data: <i>2001/16</i> 60/050,295 <i>3738</i> <i>09/244,648</i> 20 June 1997 (20.06.97) US <i>6/13/225</i> (71)(72) Applicants and Inventors: FARRINGTON, Alfred [US/US]; Suite 311, 9454 Wilshire Boulevard, Beverly Hills, CA 90212 (US). HUANG, Frank, K. [US/US]; 1259 Balboa Court, Sunnyvale, CA 94086 (US). (74) Agents: SHAPIRO, Steven, E. et al.; Mitchell, Silberberg & Knapp LLP, 11377 West Olympic Boulevard, Los Angeles, CA 90064 (US).		(81) Designated States: US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: BONE GRAFTING MATERIAL

(57) Abstract

The application relates to a synthetic bone grafting powder mix comprising a calcium compound and protein. Preferably, the ratio by weight of the calcium compound to protein is between 90:10 to 70:30. Further, the preferred calcium compound comprises one of the following: (a) Calcium Phosphate ($\text{Ca}_3(\text{PO}_4)_2$); (b) Calcium Carbonate ($\text{Ca}(\text{CO}_3)$); (c) Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$); (d) Monelite (CaHPO_4); or (e) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

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BONE GRAFTING MATERIAL

I. BACKGROUND OF THE INVENTION

A. Field of the Invention

5 The present invention relates to a challenging aspect of synthetic bone grafting in medicine by developing a material that mimics real bone. Ultimately, the implanted material will either be replaced or incorporated by new, natural bone. Hydroxyapatite, a form of calcium phosphate, can be used as a bone graft, but implantation of this material results in no resorption, a requirement for the
10 incorporation of new, natural bone. Small crystals of calcium phosphate compounds have also been used for this purpose, but the material does not have the structural strength to remain within the site of implantation. It is resorbed too quickly to allow for the incorporation of new bone. Another problem concerning the use of calcium phosphate involves the handling of this material. The handling and shaping of
15 hydroxyapatite and small crystals of calcium phosphate compounds are extremely difficult, because these materials lack malleability, cohesiveness and the ability to adhere to bone surfaces.

Our material can replace hydroxyapatite and small crystals of calcium
20 phosphate as bone grafting material. It has cohesiveness, malleability, and structural strength, which are qualities that can improve the task of bone grafting. The malleability allows for medical professionals to handle and shape the material with

ease, facilitating bone grafting procedures. The cohesiveness and structural strength of the material increase its chance for success in adhering to the bone defect site, resulting in a higher possibility for new bone to replace or incorporate the bone grating material within the defect site.

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II. SUMMARY OF THE INVENTION

A challenging aspect of synthetic bone grafting in medicine is developing a material that can mimic the normal characteristics of healthy bone. Hydroxyapatite, a form of calcium phosphate, can be used as a bone graft, but implantation of this material results in no resorption, a requirement for the incorporation of new, natural bone. Small crystals of calcium phosphate compounds have also been used for this purpose, but the material does not have the structural strength to remain within the site of implantation. It is resorbed too quickly to allow for incorporation of new bone. Another problem concerning the use of pure calcium phosphate involves the handling of this material. The handling and shaping of hydroxyapatite and small crystals of calcium phosphate compounds is extremely difficult, because these materials lack cohesiveness and the ability to adhere to bone surfaces.

Implantation of calcium phosphate that contains protein could promote new bone growth by allowing the body to digest the protein away and build a cavernous system within the material. In addition, calcium phosphate that contains protein has greater structural strength than any calcium phosphate compound without protein,

allowing the material to stay within the defect long enough for the body to proceed with natural bone replacement.

This document describes a material that incorporates any calcium containing
5 compound and a protein. The protein provides the strength, elasticity, and malleability of the material. It also allows for the body to resorb and replace the protein with its own pre-bone materials and use the calcium compound within the bone grafting material to deposit natural bone. Any protein can be used, although vegetable protein is preferred, such as gluten, glutenin or gliadin. Combinations of
10 different proteins can also be used.

III. BRIEF DESCRIPTION

The material of the synthetic bone graft is a mixture that contains specific amounts of any form of any calcium containing compound and protein. Vegetable
15 protein is preferred, such as gluten, glutenin and gliadin, or a combination thereof. Adding water to the mixture results in the formation of a protein matrix which incorporates the calcium containing compound. This material could be used as a bone graft for periodontal, jaw, and other bone defects.

20 IV. DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

The synthetic, bone-graft material has the following composition:

- a). 90-70% w/w any physical form of any calcium containing compound
such as:

Calcium Phosphate ($\text{Ca}_3(\text{PO}_4)_2$)

Calcium Carbonate ($\text{Ca}(\text{CO}_3)$)

5 Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$)

Monetite (CaHPO_4)

Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$)

etc.

(90-70% of a mixture of any such compounds could also suffice).

- 10 b). 10-30% w/w of protein, preferably vegetable protein (such as gluten,
glutenin, and/or gliadin, or a mixture thereof).
- c). 40-60% v/w (cc/g) water or other fluid.

The above materials can be put in a bowl or other receptacle and mixed
15 together. There is no particular order in which the materials should be introduced
into the mixture. In addition, a portion of the materials can be mixed together with
the remaining material mixed in after.

This composition produces a material that is pasty and has moderate
20 cohesiveness and elasticity. By changing the above composition, you can alter the
elasticity and hardness of the material, as needed. The material can also be
made in powder form by eliminating the water or other fluid. The powder can be

applied directly to the bone defect, as can the material which comprises water or other liquid.

Calcium phosphate materials have been known to enhance bone regeneration
5 when implanted into a bone defect site. (See, A.N. Cranin, G.P. Tobin, and J. German, *Compend. Contin. Educ. Dent.*, 1987, 8:334; R.Z. Legeros, *Adv. Dent. Res.*, 1988, 2:164; and K. deGroot, *Bioceramics of Calcium Phosphate*; CRC Press, Inc., Boca Roton, 1983.) Gluten is wheat protein that is available commercially as a food product. It is extracted and milled from wheat flour and contains two subunits
10 of wheat protein called glutenin and gliadin. Glutenin has properties that give strength and elasticity to flour dough. (See also, J.R. Whitaker and S.R. Tannenbaum, *Food Proteins*, The Avi Publishing Company, Wesport, 1977.) Gluten or glutenin provides a protein matrix in which a calcium containing compound can be incorporated. The incorporation of a calcium containing compound into gluten or
15 glutenin according to the above composition produces a paste-like material that is malleable into any shape. The material can be used as a bone graft for implantation into a bone defect site, protecting the defect site and enhancing bone regeneration.

In all cases, a bone site can be treated with or without an incision.

- 20 (a) The bone grating material described herein can be injected to a site using a syringe without incision;
- (b) Said material can be applied to the site using a spatula after incision;

- (c) User can apply said material to a site by hand after incision;
 - (d) Said material can be condensed to a site after incision; and
 - (e) Said material can be prefabricated into any shape or form and delivered and stabilized over the site with or without any cement after
- 5 incision.

In addition, the calcium compound(s) and protein mixture can be applied after incision in powder form.

- 10 Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein.

CLAIMS

We claim:

1. A synthetic bone grafting powder mix comprising:
 - (a) a calcium compound; and
 - (b) protein.
2. The mix according to claim 1 wherein the ratio by weight of the calcium compound to protein is between 90:10 to 70:30.
3. The mix according to claim 1 wherein the calcium compound comprises one of the following:
 - (a) Calcium Phosphate ($\text{Ca}_3(\text{PO}_4)_2$);
 - (b) Calcium Carbonate ($\text{Ca}(\text{CO}_3)$);
 - (c) Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$);
 - (d) Monetite (CaHPO_4); or
 - (e) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).
4. The mix according to claim 4 wherein the ratio by weight of the calcium compound to protein is between 90:10 to 70:30.

5. The mix according to claim 1 wherein the calcium compound comprises calcium and phosphorous.
6. The mix according to claim 5 wherein the calcium compound includes a plurality of molecules which each have more than one phosphorous atom.
7. The mix according to claims 5 or 6 wherein the ratio by weight of the calcium compound to protein is between 90:10 to 70:30.
- 10 8. The mix according to claim 1 wherein the calcium compound comprises calcium and phosphorous and the mix further comprises a second calcium compound comprising calcium and phosphorous.
9. The mix according to claim 8 wherein one of the calcium compounds
15 is one of the following:
- (a) Calcium Phosphate ($\text{Ca}_3(\text{PO}_4)_2$);
 - (b) Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$);
 - (c) Monetite (CaHPO_4); or
 - (d) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

10. The mix according to claim 8 wherein one of the calcium compounds includes a plurality of molecules each of which comprise more than one phosphorous atom.

5 11. A synthetic bone grafting powder mix comprising:

- (a) a plurality of calcium compounds; and
- (b) protein.

12. The mix according to claim 11 wherein the plurality of calcium compounds comprise Calcium Phosphate ($\text{Ca}_3(\text{PO}_4)_2$) and one of the following:

- (a) Calcium Carbonate ($\text{Ca}(\text{CO}_3)$);
- (b) Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$);
- (c) Monetite (CaHPO_4); or
- (d) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

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13. The mix according to claim 11 wherein the plurality of calcium compounds comprise Calcium Carbonate ($\text{Ca}(\text{CO}_3)$) and one of the following:

- (a) Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$);
- (b) Monetite (CaHPO_4); or
- (c) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

20

14. The mix according to claim 11 wherein the plurality of calcium compounds comprise Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$) and one of the following:

- (a) Monetite (CaHPO_4); or
- (b) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

5

15. The mix according to claim 11 wherein the plurality of calcium compounds comprise Monetite (CaHPO_4) and Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

16. The mix according to claims 8, 9, 10, 11, 12, 13, 14 or 15 wherein the ratio of the total weight of collective calcium compounds to the weight of the protein is between 90:10 to 70:30.

17. The mix according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 wherein the protein comprises vegetable protein.

15

18. The mix according to claim 17 wherein the vegetable protein comprises gluten.

19. The mix according to claim 17 wherein the vegetable protein comprises
20 glutenin.

20. The mix according to claim 17 wherein the vegetable protein comprises gliadin.

21. The mix according to claims 18 or 19 wherein the vegetable protein further comprises gliadin.

22. The mix according to claims 19 or 20 wherein the vegetable protein further comprises gluten.

23. The mix according to claims 18 or 20 wherein the vegetable protein further comprises glutenin.

24. The mix according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 wherein the mix is combined with a liquid.

15

25. The mix according to claim 24 wherein the liquid comprises water.

26. A method for making a bone grafting material comprising the following steps:

- 20
- (a) Put a calcium compound into a receptacle;
 - (b) put protein into said receptacle;
 - (c) put liquid into said receptacle; and

(d) mix said calcium compound, protein and liquid.

27. The method according to claim 26 wherein the ratio by weight of the calcium compound to protein is between 90:10 to 70:30.

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28. The method according to claim 26 wherein the calcium compound comprises one of the following:

10

- (a) Calcium Phosphate ($\text{Ca}_3(\text{PO}_4)_2$);
- (b) Calcium Carbonate ($\text{Ca}(\text{CO}_3)$);
- (c) Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$);
- (d) Monetite (CaHPO_4); or
- (e) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

29. The method according to claim 28 wherein the ratio by weight of the calcium compound to protein is between 90:10 to 70:30.

15

30. The method according to claim 26 wherein the calcium compound comprises calcium and phosphorous.

20 31. The method according to claim 30 wherein the calcium compound includes a plurality of molecules which each have more than one phosphorous atom.

32. The method according to claims 30 or 31 wherein the ratio by weight of the calcium compound to protein is between 90:10 and 70:30.

33. A method for making a bone grafting material comprising the following 5 steps:

- (a) Put a plurality of calcium compounds into a receptacle;
- (b) put protein into said receptacle;
- (c) put liquid into said receptacle; and
- (d) mix said calcium compounds, protein and liquid.

10

34. The method according to claim 33 wherein the plurality of calcium compounds comprise Calcium Phosphate ($\text{Ca}_3(\text{PO}_4)_2$) and one of the following:

- (a) Calcium Carbonate ($\text{Ca}(\text{CO}_3)$);
- (b) Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$);
- (c) Monetite (CaHPO_4); or
- (d) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

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35. The method according to claim 33 wherein the plurality of calcium compounds comprise Calcium Carbonate ($\text{Ca}(\text{CO}_3)$) and one of the following:

- (a) Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$);
- (b) Monetite (CaHPO_4); or
- (c) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

20

36. The method according to claim 33 wherein the plurality of calcium compounds comprise Fluorapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$) and one of the following:

- (a) Monetite (CaHPO_4); or
- (b) Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

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37. The method according to claim 33 wherein the plurality of calcium compounds comprise Monetite (CaHPO_4) and Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$).

38. The method according to claims 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36 or 37 wherein the ratio of the total weight of collective calcium compounds to the weight of the protein is between 90:10 to 70:30.

39. The method according to claims 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, or 38 wherein the protein comprises vegetable protein.

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40. The method according to claim 39 wherein the vegetable protein comprises gluten.

41. The method according to claim 39 wherein the vegetable protein comprises glutenin.

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42. The method according to claim 39 wherein the vegetable protein comprises gliadin.

43. The method according to claims 40 or 41 wherein the vegetable protein further comprises gliadin.

44. The method according to claims 41 or 42 wherein the vegetable protein further comprises gluten.

10 45. The method according to claims 40 or 42 wherein the vegetable protein further comprises glutenin.

46. The method according to claims 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44 or 45 wherein the liquid comprises water.

15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12605

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61P 2/28

US CL : 623/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 433/199.1 228.1; 523/116; 623/16

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,455,231 A (CONSTANTZ et al) 03 October 1995, entire document.	1, 3, 5, 6, 8-15 ----- 2, 7, 16, 26-37
X --- Y	US 4,869,906 A (DINGELDEIN et al) 26 September 1989, entire document.	1, 3, 5, 6, 8-13 ----- 2, 7, 16, 26-35
X	US 5,580,623 A (FULMER et al) 03 December 1996, entire document.	1, 3, 5, 6, 8-10, 12-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

15 SEPTEMBER 1998

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23 OCT 1998

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12605

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 4
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 4 depends upon itself, and thus its scope could not be determined.

3. ☒ Claims Nos.: 17-25, 38-46
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12605

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS

Search Terms: (calcium phosphate and/or (calcium carbonate or CaCO_3) and/or (fluorapatite or fluoroapatite) and/or (monetite or CaHPO_4) and/or (hydroxylapatite or hydroxyapatite)) and protein# and bone#